REMARKS

This amendment is undertaken to present the claimed subject matter in a format that more particularly points out and distinctly claims that which Applicants regard as their Invention.

Claim 1 is amended to delete extraneous references to the term "group" regarding the members of the variable Ar, and to variables R^7 and R^8 that are not constituents of the formula for compound I. Claim 1 is also amended to properly recite its constituent elements.

Claim 2 is amended to distinctly describe what the original "and/or" construction thereof provided for.

Claims 3, 7, 9, 11-12, 15-19, 22-23, 26-27, 30-32, 34-35, 37, 40-41, 44-46, and 48-49 are amended to obviate the rejection under 35 USC §112, second paragraph regarding the use of comprising language in a Markush claim, and to properly recite constituent elements.

Claim 4 is amended to correct a grammatical matter.

Claim 21 is amended to include the appropriate definitions for variables therein and to properly recite its constituent elements.

Claims 25, 29 35, 43 and 49 are amended to delete improper further defining of members thereof. The further defining is made the subject matter of new claims 73-75.

Claims 34 and 48 are also amended to correct typographical errors in the term "heteroaryl".

Claim 36 is amended to be dependent from claim 21.

Claims 51, 53-55 58 and 61 are amended to obviate any rejection under 35 USC §112, second paragraph regarding the lack of use of therapeutic amounts in the claims.

Claims 55 58 and 61 are also amended to obviate any rejection under 35 USC §112, second paragraph regarding there being no specific designation of the condition treatable

according to the invention in the claims. Thus, Asthma is added as a specific condition to the claims.

Claim 76 is added to retain the subject matter of cancelled claim 13.

Support for the amendments is found throughout the specification. No new matter is added. Thus, the entry of the Amendment is requested.

I. Finality of Restriction Requirement

In the instant case, the Examiner has maintained the restriction requirement as Applicants have allegedly "presented mere argument without factual evidence that the instant variable ring compounds share a substantial feature disclosed as being essential to the claimed utility." Paper No. 8, page 2, first paragraph. More particularly the Examiner stated that

> Applicants attention is drawn to MPEP 803.02 restriction of Markush claims: "Broadly, unity of invention exists where compounds included within a Markush group (1) share a common utility ***and*** (2) share a substantial structural feature disclosed as being essential to that utility". The restriction was made based on that each different core structure have diverse utility for example, the pyrrolidinyl ring compounds are intermediates for making antibacterial (see US 5,342,844 col.16 example J, the seven membered ring compounds are antimicrobial (see CA128). Applicants presented mere arguments ***without*** factual evidence that diverse ring members responsible for diverse utility are obvious variants for the tryptase inhibition. Further, the specification on pages 147-148 disclosure support that this exclusive tryptase inhibitory activity is limited only to the piperidinyl compounds.

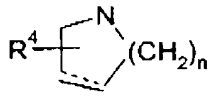
Paper No. 8, page 2, second paragraph.

Applicants traverse the aforesaid.

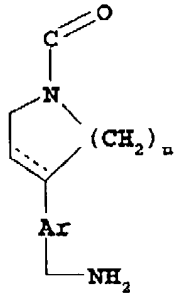
First, Applicants submit that the Examiner's original basis for the restriction requirement was proffered without any articulated legal foundation for carving up a Markush claim into groups I and II. Thus, Applicants submit that their response to that issue was sufficient, particularly given that the Examiner did not present any evidence in support of the restriction of Markush claimed subject matter. Furthermore, Applicants in responding to the original basis addressed what the legal criteria for a restriction requirement are pursuant to In re Harnisch, 206 USPQ 300, 305 (CCPA 1980), and noted that " the Examiner has no basis foundation for dissecting Applicants' compounds ... relying on differences in elements, bonding arrangements and chemical properties of group I and II." Applicants' response

mailed March 7, 2003 at page 3, last full paragraph.

Second, Applicants submit that the Examiner improperly made the present Restriction Requirement final, as the Examiner has raised presented new arguments and evidence in support of the present Restriction Requirement. In the instant case, the Examiner should have allowed Applicants with an opportunity to respond to the new arguments and evidence before making the Restriction Requirement final. In particular, the Examiner refers to US 5,342,844 and CA128 as references that should different ring sizes in compounds give rise to utilities that differ from the ring constituent in Applicants' Markush claimed invention. However, the references are not directed to compounds that fit within Applicants' core, and the rings referred to represent only a fraction of the core that applicants had previously set out. Thus, the references are not fairly citable against Applicants' claimed invention. The Examiner also mischaracterizes what Applicants' specification by stating that "pages 147-148 disclosure support that this exclusive tryptase inhibitory activity is limited only to the piperidinyl compounds." No where on pages 147-148 is there a representation that tryptase inhibitory activity is limited to piperdinyl compounds. In fact, the specification repeatedly notes that the invention contemplates the below variable moiety where n is 0-4 as part of the



substituted whole core shown in Applicants'response mailed March 7, 2003 at page 4, top structure, i.e.,



Applicants also submit that the Examiner has not adhered to the requirement of MPEP 707.07(f), i.e., "[w]here the applicant traverses any rejection, the examiner should, if ..; she repeats the rejection, take note of the applicant's argument and answer the substance of it." In the instant case the Examiner, in fact, mischaracterized Applicants' traversal as being based on the ground "that the claims are drawn to Markush format thus variable ring size is not repugnant to principles of scientific classification." Paper No. 8, page 2, first paragraph.

In fact, Applicants traversal discussed a plethora of issues, and in particularly, regarding the applicability of the case law In re Harnisch, 206 U.S.P.Q. 300 (CCPA 1980), Ex parte Holt and Randell, 214 USPQ 381, 386 (Bd. App., 1982), and Ex parte Dahlen and Zwilgmeyer, 42 USPQ 208, (Bd. App., 1938). However, the Examiner failed to address a single one of these cases.

Applicants also are truly mystified to the basis for a restriction to group IV. The Examiner alleges that such is proper as

> ... composition of multiple active ingredients are patentably distinct and unrelated to the other groups has been clearly delineated with factual evidence in the previous office action (see p.3 office action and citation of PTO-892). It was clearly evidenced by CA 132 that the combination of tryptase inhibitor and steroids would lead to synergistic decrease of mast cell activation while combination of tryptase inhibitor with adrenergic compounds (CA 110) would be counteracting on the smooth muscle relaxation. Therefore, not only combination of active ingredients is not obvious variants of single active ingredient composition but also such combination ***do not share any commonality*** of utility without specifically naming the class of active ingredients to be combined.

Paper No. 8, page 2, third paragraph.

In particular, Applicants submit that any composition that would contain a novel compound of group I or II should likewise be novel regardless of whether an additional agent provides overall additive or decrease activity. The novelty arises in the composition containing the novel ingredient and not relative to its activity. Such a position has no legal support where one of the constituents of the compositions is novel.

Applicants also take issue with the Examiner's assertion that

> ... there could have been no patentability of all the claims over US 5,342,844 col.16 example J because example J is an N- benzyl protected compound of the claims while the claims are drawn to the alternative conventional N-benzoyl protected compounds. A clear establishment of prima facie obviousness over the variation of N-protecting compounds.

Paper No. 8, page 3, paragraph spanning from page 1.

Applicants traverse the aforesaid statement as compound J of US 5,342,844 is only an intermediate, has no therapeutic activity disclosed regarding it, and no teaching is provided showing that the methylene between the phenyl and nitrogen of the pyrrolidine should be replaced by a carbonyl. Applicants submit that such issues do not establish a prima facie case of obviousness of Applicant's claimed compounds over compound J.

In view of the aforesaid, Applicants respectfully request the reconsideration of the

finality of the restriction requirement and request that the Examiner specifically address the issues raised regarding the propriety of the restriction requirement.

II. Provisional Election

Applicants acknowledge that there was an error in their provisional election referring to both groups I and II. Applicants acknowledge that group I should have been referred to in the first line of the election. Applicants thank the Examiner for correctly deducing that group I should be examined, and proceeding so.

III. Rejection of Claims under 35 USC § 112, Second Paragraph.

The Examiner rejected claims 1-49 for employing the "comprising" language in the claims. Applicants traverse this rejection. Applicants submit that the amendment of the claims has obviated this rejection.

The Examiner rejected claims 51-52 for not defining the amount of compound that would be therapeutically useful in the claims. Applicants traverse this rejection. Applicants submit that the amendment of the claims has obviated this rejection.

The Examiner rejected claims 55-63 for not defining the condition that would be treatable according to the invention. Applicants traverse this rejection. Applicants submit that the amendment of the claims has obviated this rejection.

In view of the above amendments to the claims, Applicants respectfully request the reconsideration and withdrawal of the rejections under 35 USC §112, second paragraph.

IV. Rejection of Claims under 35 USC § 103(a) over Pieper et al.

The Examiner alleges that the Pieper et al. discloses compounds that could be modified to arrive at Applicants' claimed compound.

Applicants traverse the rejection. Specifically the Examiner fails to recognize to key aspects of the Pieper et al. reference. For one Pieper et al. teaches compounds for a distinctly different indication than that of Applicants' compounds, and that there is no motivation to modify the Pieper et al. compounds to arrive at Applicants' compounds. More importantly,

Pieper et al. teahes a critical linkage for its compounds, i.e., it must have a nitrogen for bonding moiety E thereof to moicty D. See col. 1, lines 63-68. This linkage therefore obviates the Examiners suggestion that a carbon bond would be as acceptable as the the nitrogen bonds shown. Pieper et al. teaches away from sucha nd thus, it is improper to suggest that one would do so with such a contrary teaching. In view of the aforesaid Applicants respectfull7y request the reconsideration and withdrawal of the rejection over Pieper et al.

V. Rejection of Claims under Judicially created Doctrine of Obviousness-Type Double Patenting

Applicants acknowledge the art cited by the Examiner and aver that as part of the art cited against them is a pending application that the instant rejection is provisional, i.e., cannot be established until allowable subject matter would be allowable. If such art were to remain the only outstanding matter in the prosecution of this case, Applicants will file a terminal disclaimer to obviate this rejection. Consequently, Applicants request that this basis for rejection be kept in abeyance until the remaining issues are decided.

In view of the aforesaid Applicants submit that the Claims as amended are believed to be in condition for allowance, and early and favorable action on the claims is earnestly solicited.

Respectfully submitted,

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